IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Hillman et al.

Title: TUMORIGENESIS PROTEIN

Serial No.:   09/848,915   Filing Date: May 4, 2001

Examiner: Huff, S.   Group Art Unit: 1642

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard;
2. Reply Brief (25 pp., in triplicate);
3. Declaration of John C. Rockett, Ph.D., under 37 C.F.R. §1.132, with Exhibits A - Q (in triplicate);
4. Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. §1.132, with Exhibits A - E (in triplicate);
5. Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. §1.132 (in triplicate);
6. Ten (10) References (1 - 10) (in triplicate); and
7. Request for Oral Hearing (1 pg.).

The Fees as calculated as follows:

  _X_   Fee for Request for Oral Hearing under 37 C.F.R. § 1.17(d): $ 290.00
  _X_   Please charge Deposit Account No. 09-0108 the amount of :   **$ 290.00**

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. **09-0108**. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,

INCYTE CORPORATION

Date: ____February 3, 2004____

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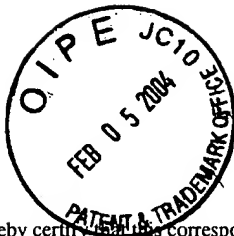**Customer No.: 27904**
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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REPLY BRIEF ON APPEAL

Sir:

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated December 3, 2003 ("the Examiner's Answer") in the above-identified application.

In the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of Claims 1 and 15 under 35 U.S.C. § 112, first paragraph for alleged lack of written description of the claimed polypeptide variants and fragments.

(1) maintained the rejection of Claims 1, 2, 15, and 16 under 35 U.S.C. § 101 on the grounds that the claimed polypeptide allegedly does not possess a specific and substantial asserted utility or a well established utility; and

(2) maintained the rejection of Claims 1, 2, 15, and 16 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement because of the invention's alleged lack of utility.

Issue One: WRITTEN DESCRIPTION REJECTION OF CLAIMS 1 and 15

I.   Comments on the Rejection

The Examiner's Answer states that "Claim 1 is broadly drawn to 'a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1'

and **biologically-active** and immunogenic fragments. Claim 1 is broadly drawn to a polypeptide comprising an amino acid sequence selected from a naturally-occurring amino acid sequence having at last 90% sequence identity to the sequence of SEQ ID NO:1, **biologically-active fragment** of the amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of the amino acid sequence of SEQ ID NO:1." (Examiner's Answer, page 3, emphasis added.) Appellants note that the appealed claims do not recite "biologically-active fragments" or "biologically-active fragment." Appellants assume that the Examiner used the phrases "biologically-active fragments" and "biologically-active fragment" inadvertently.

The Examiner stated that "[t]he specification as filed does not provide adequate written description support for an **antibody** to a polypeptide having at least 90-99% sequence identity to SEQ ID NO:1." (Examiner's Answer, page 4, emphasis added.) Appellants note that the appealed claims do not recite an antibody, and therefore assume that the Examiner made the statement inadvertently.

II.   Written Description of the Claimed Polypeptide Variants and Fragments

Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the Specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Appellants were in possession of the claimed polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1 or the claimed immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1.

The Examiner alleges that "there is insufficient written description as to the identity of a polypeptide having at least 90-99% sequence identity to SEQ ID NO:1 that would still maintain the function of the polypeptide." (Examiner's Answer, page 4.) The Examiner's Answer further alleges that "[w]ith respect to fragments, there is not guidance as to which portion of the polypeptide is functional or what function the fragment is supposed to possess" and that "[i]n view of many fragments that are encompassed by the claims and in view of the lack of any guidance as to what is 'functional', applicant has not shown possession of 'fragments'." (Examiner's Answer, pages 4-5.)

In the Examiner's Answer, the Examiner ignores the claim limitations of "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1" and "an immunogenic fragment of a polypeptide having an amino

acid sequence of SEQ ID NO:1" and attempts to introduce a limitation of biological "function" to the polypeptide variants and fragments, a limitation which is not present in the rejected claims. The Examiner ignores the limitation that the claimed polypeptide comprises a naturally-occurring amino acid sequence or is a fragment of a naturally-occurring amino acid sequence.

The Examiner's position is clearly contrary to the USPTO's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described** in the specification, then the adequate description requirement is met. (citations omitted, emphasis added)

There simply is no requirement that the claims recite particular variant and fragment polypeptide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polypeptide variants and fragments are defined in terms of SEQ ID NO:1 ("An isolated polypeptide selected from the group consisting of: . . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1, and c) an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:1." Because the polypeptide variants and fragments are defined in terms of SEQ ID NO:1, the precise chemical structure of every polypeptide variant and fragment within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Appellants further submit that given the polypeptide sequence of SEQ ID NO:1, it would be redundant to list specific fragments. The structure of SEQ ID NO:1 provides the blueprint for all fragments thereof. Listing all possible fragments of SEQ ID NO:1 is, thus, a superfluous exercise which would needlessly clutter the Specification. As long as the polypeptide variants and fragments contain naturally-occurring sequences, they are useful in toxicology testing. Their "function," whether the same or different than that of SEQ ID NO:1, is immaterial, given the description in the Specification and what is known to one of

skill in the art (see, infra, Issue Two, Utility Rejection of Claims 1, 2, 15, and 16). Accordingly, the Specification provides an adequate written description of the recited polypeptide.

III. Sequence Comparison Methods

The Examiner's Answer repeated the arguments made in the Final Office Action regarding the Brenner et al. paper ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Reference No. 1 attached to this Reply Brief). (Examiner's Answer, pages 6-7, see also Final Office Action, pages 2-3.) Appellants addressed these arguments in the Appeal Brief (pages 8-12), but the Examiner's Answer did not refer to or mention any of Appellants' Appeal Brief statements regarding the Brenner et al. paper. Therefore, for the Board's convenience, Appellants again address the Examiner's arguments (made both in the Final Office Action and in the Examiner's Answer) regarding the Brenner et al. paper.

The claims at issue do not describe a genus which could be characterized as having "highly diverse functions." (Examiner's Answer, page 4.) Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078) (Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, inter alia, to proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as tumorigenesis proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, a polypeptide "comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1," (note that SEQ ID NO:1 has 195 amino acid residues). This variation is far less than that of all potential tumorigenesis

proteins related to SEQ ID NO:1, i.e., those tumorigenesis proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

The Examiner disputes the evidence of the Brenner et al. paper, arguing that "Brenner et al. merely point out (page 6076, 2nd column, 2nd paragraph) that a 30% identity was a reliable threshold for plotting the percent identity of unrelated proteins in a particular database- the PDB90D-B (Protein Data Bank comprising domains with were all less than 90% identical) which contains over 2000 protein domains- (page 6074, 2nd column, 2nd paragraph, and Figure 3). In contrast, appellant is comparing the sequence identity of an unknown protein to the sequence of BUP. Thus, from a statistical view, one of ordinary skill in the art would conclude that appellant does not have the quantity of data to extrapolate the results of Brenner et al." (Examiner's Answer, pages 6-7.)

The Examiner appears to have misunderstood the significance of the Brenner et al. paper's findings. The Brenner et al. paper does not describe a method for figuring out functions of unknown proteins, The Brenner et al. paper evaluates known methods of sequence comparison using the SCOP data set of proteins whose functions are already known independently of sequence comparison methods. One does not need independently to come up with a new SCOP-sized data set to use the conclusions of the Brenner et al. paper, that sequence comparison methods are reliable in determining relationships between proteins and that at least 30% identity over at least 150 amino acid residues is a good cutoff value.

The SCOP database used in the Brenner et al. paper is a database of proteins with known structures. In the Brenner et al. paper the SCOP database was used to test the reliability of sequence comparison methods. The Brenner et al. paper does not discuss predicting "functional similarity," but rather evolutionary relationships. Use of this database of proteins with known structures allowed the authors to determine whether homologies predicted from the sequence comparison methods tested in the article were truly similar structurally. The Brenner et al. paper is not trying to predict relationships between proteins; the Brenner et al. paper is evaluating known methods of predicting protein relationships. One cannot test the ability of sequence comparison methods in predicting actual structural homology if one starts with protein sequences whose structures were not already known previously and independently of the sequence comparison.

The Examiner further contends that "Brenner et al. teach that high percent identity does not necessarily identify related proteins (Figure 2) wherein the principal reasons percentage identity does so poorly seem to be that is it ignores information about gaps and about the

conservative or radical nature of residue substitutions (page 6076, 2nd column, 1st paragraph)."
(Examiner's Answer, page 7.)

The Examiner appears to draw the incorrect conclusion from Figure 2 of the Brenner et
al. paper with respect to its relevance to the reliability of the patent application's conclusion that
the instant SEQ ID NO:1 polypeptide is related to the murine BUP protein, and that the
polypeptide variants at least 90% identical to the SEQ ID NO:1 polypeptide are related to the
SEQ ID NO:1 polypeptide, based on their percentage identity. Figure 2 of the Brenner et al.
paper gives an example of "[u]nrelated proteins with high percentage identity." (Brenner et al.,
page 6075, Figure 2.) Hemoglobin β-chain (1hdsb) and cellulase E2 (1tml_) "have 39% identity
over 64 residues, a level which is often believed to indicative of homology. Despite this high
degree of identity, their structures strongly suggest that these proteins are not related." (Brenner
et al. , page 6075, Figure 2.) Figure 2 of Brenner et al. paper does not support the Examiner's
arguments for the following reasons. The percentage identity over sequence length for the
alignment of the SEQ ID NO:1 polypeptide with respect to BUP, and for the alignment of the
SEQ ID NO:1 polypeptide variants with respect to the SEQ ID NO:1 polypeptide is much higher
than that for the alignment of hemoglobin and cellulase. The SEQ ID NO:1 polypeptide and
BUP share 89% identity over 195 amino acid residues. The SEQ ID NO:1 polypeptide and its
90% variants share at least 90% identity over 195 amino acid residues. These percentage
identity over sequence length values (89% over 195 amino acid residues and at least 90% over
195 amino acid residues) are much greater than those between hemoglobin and cellulase (39%
over 64 amino acid residues). It is noted that the hemoglobin and cellulase example in Figure 2
does not meet the cutoffs taught in the Brenner et al. paper, i.e., that "30% identity is a reliable
threshold for this database only for sequence alignments of at least 150 residues" and "it is
probably necessary for alignments to be at least 70 residues in length before 40% is a reasonable
threshold." (Brenner et al., page 6076.) These cutoffs were determined from the analysis
summarized in Figure 3 of the Brenner et al. paper. Therefore it is more likely than not that the
claimed SEQ ID NO:1 polypeptide is related to murine BUP and that the 90% variants of the
SEQ ID NO:1 polypeptide are related to the SEQ ID NO:1 polypeptide.

The Examiner further cited Skolnick et al. in the Examiner's Answer (page 4) as teaching
that "the skilled artisan is well aware that assigning functional activities for any particular protein
or family based upon sequence homology is inaccurate." (Examiner's Answer, page 4.)
However, Skolnick et al. disclose that there are only 30-50% of proteins whose function cannot
be assigned by any current methods (page 37, col. 2). This makes it more likely than not that the

claimed SEQ ID NO:1 polypeptide, which has 89% sequence identity to murine BUP, and the claimed polypeptide variants, which have at least 90% sequence identity to the SEQ ID NO:1 polypeptide, are among the group which can be properly annotated.

Moreover, Appellants note that it is well known in the art that sequence similarity is predictive of similarity in functional activity. Hegyi and Gerstein ("Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins," Genome Research (2001) 11: 1632-1640; Reference No. 2; previously also cited in the Appeal Brief) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Reference No. 2, page 1635.) Hegyi and Gerstein also conclude that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the same in this case was 91%." (Reference No. 2, page 1636.) Hegyi and Gerstein (page 1632) further note that

> Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found that precise function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

The claimed SEQ ID NO:1 polypeptide shares 89% sequence identity with murine BUP, and the claimed polypeptide variants share more than 90% sequence identity with the SEQ ID NO:1 polypeptide, well above the thresholds described in the Hegyi and Gerstein article (Reference No. 2) cited above. Therefore, there is a reasonable probability that the SEQ ID NO:1 polypeptide would have the same function as murine BUP and that the SEQ ID NO:1 polypeptide variants would have the same function as the SEQ ID NO:1 polypeptide.

Furthermore, if the Examiner is alleging that the "highly diverse" nature of the claimed genus is that the claimed polypeptide variants and fragments have different "functions" from SEQ ID NO:1, Appellants repeat that function is immaterial to the written description of the claimed polypeptide, given the description in the Specification and what is known to one of skill in the art. The written description describes polypeptides comprising a naturally-occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1 and immunogenic fragments of a polypeptide having an amino acid sequence of SEQ ID NO:1. As

the claimed variants and fragments are not described by their having the same "function" as SEQ ID NO:1, the Examiner's arguments regarding "function" are not relevant to the written description issue. It is routine to calculate percentage identity. It is routine to use naturally-occurring polypeptides in toxicology testing. "Function" is irrelevant to the use of the claimed polypeptide in toxicology testing. (See infra, Issue Two, Utility Rejection of Claims 1, 2, 15, and 16.)

Issue Two: UTILITY REJECTION OF CLAIMS 1, 2, 15, and 16

I.   Comments on the Utility Rejection

The Examiner's Answer stated that "[t]he specification asserts the following utilities for the claimed **antibodies** . . . " and "the asserted utility of the claimed antibodies . . ." (Examiner's Answer, pages 5-6, emphasis added1.) Appellants note that the appealed claims are not directed to antibodies, and therefore assume that the Examiner made the statements inadvertently.

The Examiner's Answer stated that "[t]his argument has been fully considered but is not deemed persuasive because such analysis, in the absence of any known role of HTAP, is considered to be further research on **NHT** itself, to determine the role, function and properties of the protein." (Examiner's Answer, page 12, emphasis added.) Appellants note that the specification does not recite the term "NHT", and therefore assume that the Examiner used the term "NHT" inadvertently.

II.   Submission of Declarations and References

Appellants are submitting with this Reply Brief (in triplicate) Declarations under 37 C.F.R. § 1.132 of John C. Rockett, Ph.D. (hereinafter the "Rockett Declaration"), of Tod Bedilion, Ph.D. (hereinafter "the Bedilion Declaration"), and of Vishwanath R. Iyer, Ph.D. (hereinafter the "Iyer Declaration"), and seven (7) references published before or shortly after the March 20, 1997 filing date of the priority Hillman '260 application. As we will show, the Rockett Declaration, the Bedilion Declaration, the Iyer Declaration, and the accompanying references show the many substantial reasons why the Examiner's positions and arguments with respect to the use of the SEQ ID NO:1 polypeptide in gene and protein expression monitoring applications are without merit.

Appellants note that the submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

III. Utility of the Claimed Polypeptide in Toxicology Testing

The Examiner's Answer asserts that the utilities of the claimed polypeptide in expression profiling and toxicology testing would allegedly not have been recognized by one of skill in the art as well-established at the time of filing (Examiner's Answer, e.g., pages 8-9). Appellants submit three additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and seven (7) scientific references published before or shortly after the March 20, 1997 priority date of the instant application. The previously submitted Furness Declaration, as well as the currently submitted Rockett Declaration, Bedilion Declaration, and the Iyer Declaration, and the seven (7) references fully establish that, prior to the March 20, 1997 filing date of the priority Hillman '260 application, it was well-established in the art that:

> expression analysis is useful, inter alia, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

> expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;

> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

> antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such antibodies generate a signal that is specific to the protein, that is, produce a gene-specific expression signal;

> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

> failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and

failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

Appellants file herewith:

1.   the Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with Exhibits A-Q (hereinafter the "Rockett Declaration");

2.   the Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132 (hereinafter the "Bedilion Declaration");

3.   the Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E (hereinafter the "Iyer Declaration"); and

4.   Seven (7) references published before or shortly after the March 20, 1997 filing date of the priority Hillman '260 application,:

a)   PCT application WO 95/21944, SmithKline Beecham Corporation, Differentially expressed genes in healthy and diseased subjects (August 17, 1995) (Reference No. 3)

b)   PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995) (Reference No. 4)

c)   M. Schena et al., Quantitative monitoring of gene expression patterns with a complementary DNA microarray, Science 270:467-470 (October 20, 1995) (Reference No. 5)

d)   PCT application WO 95/35505, Stanford University, Method and apparatus for fabricating microarrays of biological samples (December 28, 1995) (Reference No. 6)

e)   U.S. Pat. No. 5,569,588, M. Ashby et al., Methods for drug screening (October 29, 1996) (Reference No. 7)

f)   R. A. Heller al., Discovery and analysis of inflammatory disease-related genes using cDNA microarrays, Proc. Natl. Acad. Sci. USA 94:2150 - 2155 (March 1997) (Reference No. 8)

g)   PCT application WO 97/13877, Lynx Therapeutics, Inc., Measurement of gene expression profiles in toxicity determinations (April 17, 1997) (Reference No. 9)

In his Declaration, Dr. Rockett explains the many reasons why a person skilled in the art in 1997 would have understood that any expressed polypeptide or expressed polynucleotide is

useful for a number of gene and protein expression monitoring applications, e.g., in 2-D PAGE technologies or cDNA microarrays, in connection with the development of drugs and the monitoring of the activity of such drugs. (Rockett Declaration at, e.g., ¶¶ 10-18).

It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state. [Rockett Declaration, ¶ 11.]

Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s. [Rockett Declaration, ¶ 14.]

It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology. [Rockett Declaration, ¶ 18.][1]

In his Declaration, Dr. Bedilion explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. (Bedilion Declaration, e.g., ¶¶ 4-7.) In his Declaration, Dr. Iyer explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.)

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 7) and published PCT applications WO 95/21944 (Reference No. 3), WO 95/20681 (Reference No. 4), and WO 97/13877 (Reference No. 9).

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[1] "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

<u>U.S. Pat. No. 5,569,588</u> ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 9, 1995, describes an expression profiling platform, the "genome reporter matrix," which is based upon the measurement of protein expression levels. The '588 patent further describes use of nucleic acid microarrays to measure transcript expression levels, making clear that the utility of comparing multidimensional expression data sets equally applies to protein expression data and transcript expression data.

The '588 patent speaks clearly to the usefulness of such expression analyses, particularly but not exclusively protein expression profiling, in drug development and toxicology, particularly pointing out that a protein's failure to change in expression level is a useful result. Thus, with emphasis added,

[The invention provides] methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to <u>obtain a drug response profile</u> which provides a model of the transcriptional responsiveness of said organism to the candidate drug. [abstract]

The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising <u>substantially all targets in a pathway [or] organism</u>. [column 1]

The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. <u>Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes.</u> We term such a substantially comprehensive ensemble a genome reporter matrix. [column 2]

Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects. [columns 2-3]

Furthermore, <u>it is not necessary to know the identity of any of the responding genes</u>. [column 3]

[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical. [column 4]

The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters. [column 4]

A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included. [columns 6-7]

In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form <u>reference response profiles</u> that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . <u>The drug induces a complex response pattern</u> of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug. [columns 7-8]

In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, <u>under conditions where each of the transcripts hybridizes with a corresponding one</u> of the probes to form

hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile. [column 8]

The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses. [column 8]

Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli. [column 9]

The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s). [column 9]

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of nucleic acid microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]

The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof. [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term "disease" or "disease state" refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term "solid support" refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By "EST" or "Expressed Sequence Tag" is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences

in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Applicants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484, issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression patterns, or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

[The invention provides a] method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens. [abstract]

[W]e see each individual gene product as a "pixel" of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual "pixels" of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood. [page 2]

The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts. [page 6]

High resolution analysis of gene expression be used directly as a diagnostic profile. . . . [page 7]

The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed. [page 7]

The invention . . . includes a method of comparing specimens containing gene transcripts. [page 7]

The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript sequences, which indicate the differences in the number of gene transcripts between the two specimens. [i.e., the results yield analogous data to microarrays] [page 8]

Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made. [page 8]

In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities. [page 9]

In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . [page 9]

[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. [pages 9-10]

The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as "gene transcript image analysis" or "gene transcript frequency analysis". The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism. [page 11]

The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few. [page 12]

[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates. [page 12]

For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . . [page 12]

In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . [page 12]

In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond. [page 12]

In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models. [page 14]

In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition. [page 14]

An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined. [page 15]

[T]his research tool provides a way to get new drugs to the public faster and more economically. [page 36]

In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker. [page 38]

[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of _toxicity by correlation_ with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients. [page 39]

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), filed on October 11, 1996 and published on April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the WO 97/13877 publication describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates. [Field of the invention]

An object of the invention is to provide _a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles_, in in vitro or in vivo test systems. [page 3]

Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals. [page 3]

The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such _profiles may be compared_ with those from tissues of control organisms at single or multiple time points to _identify expression patterns predictive of toxicity_. [page 3]

As used herein, the terms "gene expression profile," and "gene expression pattern" which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . . .. Preferably, the total number of sequences determined is at least 1000; _more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand_. [page 7]

The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues

of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . [page 7]

In light of this and other evidence of the state of the art, one of ordinary skill in the toxicology arts would conclude that "[i]t is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new gene or protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the gene and/or protein in expression profiling studies in toxicology." (Rockett Declaration, ¶ 18.)

IV. Irrelevance of tissue distribution or disease association to utility in toxicology testing

The Examiner argues on page 6 of the Examiner' s Answer that the specification does not disclose a "specific tissue distribution" of the claimed polypeptide or a "specific disease state in which these proteins affect." In the Examiner's Answer the Examiner further argues that "the specification does not establish that the protein of SEQ ID NO:1 is expressed in any disorder in any way that is different from the way it is expressed in normal individuals." (Examiner's Answer, page 12.) These are irrelevant. Appellants need not demonstrate whether the claimed polypeptide is associated with any tissue or disease, only whether the claimed polypeptide is useful. The claimed polypeptide is useful whether or not the claimed polypeptide is associated with any tissue or disease.

The claimed polypeptide can be used for toxicology testing in drug discovery without any knowledge of tissue distribution or disease association of the claimed polypeptide. Monitoring the expression of the claimed polypeptide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the tissue distribution or disease association of the claimed polypeptide. The claimed polypeptide is useful for measuring the toxicity of drug candidates specifically targeted to other polypeptides regardless of any possible utility for measuring the properties of the claimed polypeptide.

Appellants note that monitoring the expression of the claimed polypeptide is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polypeptide is affected in any way by exposure to a test compound, and if that particular polypeptide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology

testing using expression profiling using 2-D PAGE reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from a 2-D PAGE gel in a protein expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polypeptide whose expression is being monitored.

As an example, any actin gene or histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. An actin gene or histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed actin gene or histone gene is surely an excellent subject for toxicology studies when developing drugs targeted to other genes. A drug candidate which alters expression of an actin gene or histone gene is toxic because disruption of such a constitutively expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of an actin gene or histone gene is a good measure of the toxicity of that candidate, particularly in in vitro cellular assays at an early stage of drug development. The utility of any particular human-expressed actin gene or histone gene in toxicology testing is specific and substantial because a toxicology test using that actin gene or histone gene cannot be replaced by a toxicology test using a different gene, including any other actin gene or histone gene. This specific and substantial utility requires no knowledge of the biological function or disease association of the actin gene or histone gene.

V. The claimed isolated polypeptide is useful in toxicology testing

The Examiner's Answer repeated the arguments made in the Final Office Action regarding the use of the claimed isolated polypeptide in toxicology testing. (Examiner's Answer, page 11, see also Final Office Action, page 7.) Appellants addressed these arguments in the Appeal Brief (pages 29-30), but the Examiner's Answer did not refer to or mention any of Appellants' Appeal Brief statements regarding the use of the claimed isolated polypeptide in toxicology testing. Therefore, for the Board's convenience, Appellants again address the Examiner's arguments (made both in the Final Office Action and in the Examiner's Answer) regarding the use of the claimed isolated polypeptide in toxicology testing.

The Examiner further disputes the utility of the claimed polypeptide in toxicology testing, asserting that "the uses urged by Declarant do not require isolated protein of SEQ ID NO:1," and

that "[i]n the types of analyses urged by Declarant, the proteins themselves are not isolated, nor are antibodies to specific proteins made." (Examiner's Answer, page 11.) However, the Examiner is incorrect in the assertion that an "isolated protein of SEQ ID NO:1" does not have utility in toxicology testing, for example, in 2-D PAGE analysis. The claimed isolated polypeptide is useful in toxicology testing in 2-D PAGE analyses, to identify which spot in the 2-D PAGE analysis of a biological sample corresponds to the sample-derived SEQ ID NO:1 polypeptide. For example, comigration of the known isolated SEQ ID NO:1 polypeptide with an unknown sample spot on a 2-D PAGE gel identifies that unknown sample spot as sample-derived SEQ ID NO:1 polypeptide. In another example, the isolated SEQ ID NO:1 polypeptide may be used as an immunogen for the production of antibodies which can be used to detect sample-derived SEQ ID NO:1 polypeptide on the 2-D PAGE gel.

Such uses are supported, for example, in the Furness Declaration and in the Celis et al. article (Tab D) cited in the Furness Declaration. Furness in his Declaration states that "[e]xpressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds" and "[t]he isolated polypeptide could therefore be used as a control to more accurately gauge the expression of HTAP in the sample and consequently more accurately gauge the affect of a toxicant on expression of the gene." (Furness Declaration, ¶ 12)

Furthermore, Celis et al. (Tab D cited in the Furness Declaration; Reference No. 10 in this Reply Brief) state that:

> A major obstacle encountered in building comprehensive 2-dimensional gel protein databases is identifying the large number of proteins separated by this technology. . . known proteins are identified by one or a combination of the following procedures: 1) **comigration with known proteins**, 2) **2-dimensional gel immunoblotting using specific antibodies**, 3) microsequencing. . . (Celis et al., page 2204, last paragraph in first column, emphasis added.)

> . . . we have received nearly 550 antibodies from laboratories all over the world and these are being systematically tested by 2-dimensional gel immunoblotting for antigen determination. . . . purified proteins and organelles provided by several laboratories have greatly aided identification of unknown proteins. (Celis et al., page 2204, first paragraph in second column.)

Therefore, the claimed isolated SEQ ID NO:1 polypeptide facilitates the detection and quantification of the expression of sample-derived SEQ ID NO:1 polypeptide. Such analysis

allows one to determine whether the expression of the SEQ ID NO:1 polypeptide is affected by a test compound, as this can be a measure of possible toxicity of that test compound.

Issue Three: ENABLEMENT REJECTION OF CLAIMS 1, 2, 15, AND 16

The rejection set forth in the Examiner's Answer is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Examiner's Answer, page 6). To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

For at least the above reasons, reversal of the enablement rejection is requested.

CONCLUSION

For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,
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Enclosures:

Declaration of John C. Rockett, Ph.D., under 37 C.F.R. § 1.132, with attached Exhibits A-Q

Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E

Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132

Ten (10) references:
1. S. E. Brenner et al., <u>Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships</u>, Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998) (previously also cited as Reference No. 1 in the Response to Office Action mailed January 29, 2003 and as Reference No. 1 in the Appeal Brief)
2. H. Hegyi and M. Gerstein, <u>Annotation transfer for genomics: measuring functional divergence in multi-domain proteins</u>, Genome Research 11: 1632-1640 (2001) (previously also cited as Reference No. 2 in the Appeal Brief)
3. PCT application WO 95/21944, SmithKline Beecham Corporation, <u>Differentially expressed genes in healthy and diseased subjects</u> (August 17, 1995)
4. PCT application WO 95/20681, Incyte Pharmaceuticals, Inc., Comparative gene transcript analysis (August 3, 1995)
5. M. Schena et al., <u>Quantitative monitoring of gene expression patterns with a complementary DNA microarray</u>, Science 270:467-470 (October 20, 1995)

6. PCT application WO 95/35505, Stanford University, <u>Method and apparatus for fabricating microarrays of biological samples</u> (December 28, 1995)

7. U.S. Pat. No. 5,569,588, M. Ashby et al., <u>Methods for drug screening</u> (October 29, 1996)

8. R. A. Heller al., <u>Discovery and analysis of inflammatory disease-related genes using cDNA microarrays</u>, Proc. Natl. Acad. Sci. USA 94:2150-2155 (March 1997)

9. PCT application WO 97/13877, Lynx Therapeutics, Inc., <u>Measurement of gene expression profiles in toxicity determinations</u> (April 17, 1997)

10. J.E. Celis et al., <u>Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing</u>, FASEB Journal, 5, 2200-2208 (1991) (previously also cited as Tab D attached to the Furness Declaration and as Reference No. 7 in the Appeal Brief)